New mechanism for genome unpacking in stem cells

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Scientists at Karolinska Institutet and Gurdon Institute in Cambridge, United Kingdom have identified a novel mechanism that allows pluripotent stem cells to maintain their genome in an unpacked state, and thereby maintain their unique property to give raise to all types of specialized cells in the body. The findings are presented in the journal *Nature*.

Embryonic stem cells and induced pluripotent stem cells have the capacity to give rise to all cell types present in the adult body. To maintain this immature state, genes that are turned on in specialized cells must remain inactive in pluripotent cells, but ready to be quickly activated upon maturation into, for example, a cell in the skin or liver. The genome of a cell is packed in the nucleus, in a structure called chromatin. If the chromatin packing is tight (condensed), activatory molecules cannot access parts of the genome that control the activation of genes. Thus, for a certain gene to be activated, the chromatin structure must be unpacked (decondensation).

Pluripotent stem cells are unique in that their genome is partially unpacked (chromatin decondensation), when compared to specialized cells, to allow rapid activation of differentiation genes upon a given stimuli. In this published study, an international team, lead by Professor Tony Kouzarides, at the Gurdon Institute, University of Cambridge, identified a specific enzymatic activity, called citrullination, that contributes to decondensed chromatin state in pluripotent cells.

"The genome (DNA) is highly negatively charged and is associated in the chromatin structure with proteins called histones, which are highly positively charged. We found that in pluripotent cells, citrullination reduces the charge of some histones, weakening their association with the genome and contributing to decondensation", says Gonçalo Castelo-Branco, principal investigator at Karolinska Institutet and co-first author in the study with Maria Christophorou of the Gurdon Institute.

Gonçalo Castelo-Branco's research group at Karolinska Institutet is now investigating roles for citrullination in other immature cells, such as oligodendrocyte precursors in the brain, which participate in myelin regeneration in multiple sclerosis, MS.

Research in this study was funded by grants from Cancer Research UK, the Swedish Research Council, EMBO, European Union 7th Framework Programme (FP7) Marie Curie Actions, among others grants. Gonçalo Castelo-Branco implemented parts of the study at the Gurdon Institute, where he was previously a researcher, and at Karolinska Institutet. Among the study authors is also professor John Gurdon, laureate of the Nobel Prize in Physiology or Medicine 2012. Apart from Sweden and United Kingdom, scientists from Denmark, Brasil and USA participated in the study.

More information: "Citrullination regulates pluripotency and histone H1 binding to chromatin." Maria A. Christophorou, Gonçalo Castelo-Branco, Richard P. Halley-Stott, et al.
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